REMARKS

I. Status

Claims 10, 11, and 20-33 are pending in the application. Claim 11 is currently cancelled, as discussed in greater detail below. Pursuant to the Examiner's request at page 2 of the Office Action to cancel non-elected subject matter, claim 21 is also currently cancelled without prejudice to pursuing the subject matter of such claim in any continuing application, e.g., a continuation, divisional, continuation-in-part, etc. Claims 20 and 33 are currently amended to delete the R^5 group $(C_1\text{-}C_6)$alkoxycarbonyl$(C_1\text{-}C_6)$alkylamino$(C_1\text{-}C_6)$alkyl. Claim 20 is also currently amended to correct an error of a typographical nature, which was originally presented unintentionally and in good faith. Applicants are currently presenting new claim 34, also discussed in greater detail below.

Claims 10-11 stand rejected under 35 U.S.C. § 112, ¶2. Claims 10, 11, 20, and 22-33 stand rejected under 35 U.S.C. § 112, ¶1 with regard to enablement. Claims 10, 11, 20, and 23 stand rejected under 35 U.S.C. § 103(a) over WO 98/56771 ("Bauman").

II. Interview

Applicants gratefully thank Examiner Bernhardt for her time and assistance during a telephonic interview with Applicants' attorney indicated below. During the interview, the Examiner presented certain suggestions with regard to each of the foregoing rejections, which will be readily apparent from the discussion below.

III. Claims 10 and 11 Are Definite

Claims 10-11 stand rejected under 35 U.S.C. § 112, ¶2 insofar as the Examiner continues to believe that claims 10 and 11 are "substantial duplicates" as stated at paragraph 5 in the Examiner's previous Office Action dated June 25, 2004. Applicants traverse the rejection for at least the reasons mentioned in Applicants' previous "Amendment and Response to Office Action" dated September 27, 2004.

Nevertheless, solely to advance the prosecution of the present application, Applicants are amending claims 10 and 11 in the manner suggested by the Examiner during the interview. That is, Applicants are amending claim 10 by: (i) incorporating the preamble of claim 11 in the alternative; and (ii) canceling claim 11. Support for the amendment to claim 10 can be found throughout the application, e.g., at originally filed claims 10-11.

In addition, Applicants are adding new claim 34, which defines a pharmaceutical composition comprising a compound according to claim 20, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. Support for new claim 34 can be found throughout the specification, e.g., at page 46, lines 14-20:

> For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate).

No new matter is being adding by the current amendments.

In view of the foregoing remarks, claims 10 and 34 are definite and removal of the present rejection is respectfully requested at this time.

IV. Claims 10, 11, and 22-33 Are Enabled

Claims 10, 11, 20, and 22-33 stand rejected under 35 U.S.C. § 112, ¶1 with regard to enablement. Applicants respectfully traverse the rejection.

In particular, the Examiner asserts that the claims contain subject matter what was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants traverse the rejection at least because the Examiner has not satisfied her burden of establishing that the cited claims are not enabled.

It is well settled that the PTO has the burden of giving reasons, supported by the record as a whole, why the specification is not enabling. *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976) citing *In re Armbruster*, 512 F.2d 676 (C.C.P.A. 1975). The Federal Circuit has also made it clear that enablement only requires that the specification teach those in the art to make and use the invention without undue experimentation. (Emphasis added). *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) citing *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986), cert. denied, 480 U.S. 947. "The key word is 'undue,' not 'experimentation.'" *Id.* citing *In re Angstadt*, 537 F.2d at 498, 504 (C.C.P.A. 1976). As such, not all types of experimentation is 'undue.'

At the outset, Applicants contend that the cited claims are enabled at least because the Examiner has not satisfied the above-identified burden of establishing non-enablement. Further, the Examiner has not cited *with support* how any experimentation that may be required to make and use the compounds defined by the cited claims is undue, which it is not. Indeed, the Examiner has not cited any binding precedent concerning enablement in the chemical art in support of the rejection.

Instead, the Examiner at page 4 of the Office Action cites the Board decision in the biotech art, *Ex parte Varshavsky*, for the proposition that a high level of skill in the art is not sufficient to override other Wands factors. The Examiner's citation of *Ex parte Varshavsky*, however, misses the mark because the present issue is not whether one *In re Wands* factor can "override other Wands factors" but rather whether those of skill in the art given the benefit of the present disclosure would be able to make and use the claimed compounds without undue experimentation. In essence, the Examiner's citation of *Ex parte Varshavsky* presumes that all *In re Wands* factors weigh against non-enablement with the exception of the level of skill in the art factor, which is simply not the case.

As discussed in Applicant's previous 'Amendment and Response' dated September 27, 2004, it has not been established that all *In re Wands* factors with the exception of the level of skill in the art factor weigh against non-enablement. Indeed, the Examiner in the previous Office Action dated June 25, 2004 appeared to base her opinion of non-enablement on only four of the eight *In re Wands* factors. Moreover, the four factors that the Examiner did discuss do not all necessarily support the Examiner's opinion that the claims are not enabled. For instance, with regard to the presence of working examples, the Examiner concludes in the previous Office Action that no test data has been presented - only description of testing protocols - and thus no clear evaluation of which functional groups at various positions out of the many clamed might affect potency. Applicants have, however, disclosed such test data, notably at page 46 of the specification in conjunction with 100 exemplified compounds. But for Applicants' present disclosure, those of skill in the art would not be guided to the 100 exemplified compounds and those compounds of the invention that were tested, which had an IC_{50} value of less than 25 μM in the Chemotaxis assay.

Apparently, there is more than one *In re Wands* factor in support of enablement contrary to what the Examiner presupposes.

Nevertheless, it is apparent from relevant binding precedent in the chemical art that the present specification indeed enables those of skill in the art to make and use the compounds defined by the cited claims without undue experimentation.

For example, the CCPA in *In re Angstadt* overturned a Board decision of non-enablement in determining that when a specification supplies a list of catalysts and teaches how to make and how to use them, the experimentation required to determine which catalysts will produce hydroperoxides [*ed: the desired product*] would not be undue and certainly would not "require ingenuity beyond that to be expected of one of ordinary skill in the art." *In re Angstadt* at 503 citing *Fields v. Conover*, 443 F.2d 1386, 1390-91 (C.C.P.A. 1971). Claim 1 as originally filed by the Angstadt et al. read as follows:

> A process for the oxidation of secondary and tertiary alkylaromatic compounds which comprises contacting said compounds with oxygen at an elevated temperature in the presence of a catalyst comprising a hexaalkylphosphoramide and a metal salt.

Despite the Court's acknowledgment that: (i) the art was unpredictable; (ii) applicants apparently did not disclose every catalyst which would work; (iii) applicants did not disclose every catalyst which would not work; and (iv) claim 27 literally read on thousands of metal salt complexes, it held that the specification enabled the claimed subject matter because it would be inequitable to require a patent applicant to disclose thousands of examples as such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. *Id.* at 502-503. In making this determination, the Court found it factually important that applicants provided those of skill in the art with a large but finite list of transition metal salts from which to

choose in preparing such a complex catalyst. Further, the applicants exemplified 40 runs using various transition metal salts and hexaalkylphosphoramides.

> If one skilled in this art wished to make and use a transition metal salt other than those disclosed in appellants' 40 runs, he would merely read appellants' specification for directions how to make and use the catalyst complex to oxidize the alkylaromatic hydrocarbons, and could then determine whether hydroperoxides are, in fact, formed. The process discovered by appellants is not complicated, and there is no indication that special equipment or unusual reaction conditions must be provided when practicing the invention. One skilled in this art would merely have to substitute the correct mass of a transition metal salt for the transition metal salts disclosed in appellants' 40 runs. Thus, we have no basis for concluding that persons skilled in this art, armed with the specification and its 40 working examples, would not easily be able to determine which catalyst complexes within the scope of the claims work to produce hydroperoxides and which do not.
> *In re Angstadt*, 537 F.2d 498, 502-503 (C.C.P.A. 1976).

One cannot help but notice certain similarities between the facts of *In re Angstadt* and the present case. Both *In re Angstadt* and the present case concern the chemical art. The applicants in *In re Angstadt* disclosed 40 examples; Applicants here disclose 100 examples - more than twice that of Angstadt et al. The applicants in *In re Angstadt* sought to protect a large but finite list of transition metal salts from which to choose in preparing the complex catalyst; Applicants here disclose a large but finite list of substituents for R^5. The applicants in *In re Angstadt* disclosed a general procedure for how to make the complex catalyst; Applicants here disclose seven synthetic schemes including three preparations and chemotaxis assay specifications, which certainly arms those of skill in the art with the requisite know-how to make and use the claimed compounds. In view of the cited precedent, one is hard pressed to say that the specification does not enable the claimed compounds.

Yet, the Examiner appears to base the present enablement rejection on the amount of R^5 substituents claimed insofar as the Examiner questions the efficacy of the instant scope given the supposed homogeneity of the prepared examples and the supposed lack of any test data. It is well settled, though, that an applicant only needs to enable the claimed invention. *In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991). Claim 20, one of the cited claims, defines a compound of formula I or pharmaceutically acceptable salt thereof, wherein the variables are defined. First, claim 20 does not require that the compounds have a certain efficacy. As such, the specification need not teach those of skill in the art how to make and use only compounds having a certain efficacy. In that regard, it is unclear why the Examiner singles out efficacy amongst other pharmacological (ADMET) properties. Second, the 100 examples disclosed are not homogenous insofar as a large number of the claimed R^5 groups are exemplified, contrary to the Examiner's assertion. Third, as mentioned above, test data is disclosed in the specification at page 46.

With regard to the third point above, the Examiner appears to be requiring Applicants to supply enough pharmacological data so that structure-activity trends can be evaluated. The Examiner's additional requirement, however, is inappropriate in view of the law. In *In re Angstadt*, the Court determined that such predictive data need not be disclosed:

> What the dissent seems to be obsessed with is the thought of catalysts which won't work to produce the intended result. Appellants have enabled those in the art to see that this is a real possibility, which is commendable frankness in a disclosure. Without undue experimentation or effort or expense the combinations which do not work will readily be discovered and, of course, nobody will use them and the claims do not cover them. The dissent wants appellants to make everything predictable in advance, which is impracticable and unreasonable.
> *Id.* at 504.

It appears then that the Examiner is of similar opinion as the dissent in making the statement at page

7 of the previous Office Action: "There is no reasonable assurance as to what other substituents will work as there is no test data reported..." The Examiner's position, however, is evidently not consistent with the law.

Further, the Federal Circuit has more recently confirmed the views of its predecessor court:

> . . .we do not imply that patent applicants in art areas currently denominated as "unpredictable" must never be allowed generic claims encompassing more than the particular species disclosed in their specification. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. In re Angstadt, 537 F.2d 498, 502-03, 190 U.S.P.Q. (BNA) 214, 218 (C.C.P.A. 1976). However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed.
> *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991).

In view of the foregoing remarks, it is apparent that sufficient disclosure is present here to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed.

In addition, the Examiner at page 3 of the Office Action appears to believe that not all of the claimed compounds were tested in the chemotaxis assay ("just an inference that the compounds were tested"). As such, the Examiner appears to believe that many compounds claimed were not actually made, and thus are prophetic examples. Without admitting or denying the Examiner's belief, Applicants respectfully point out that even if the examples are prophetic, it is not necessarily determinative of enablement. The Federal Circuit made this point clear in Atlas Powder Co. v. E. I. Du Pont de Nemours & Co.

> We agree with the district court's conclusion on enablement. Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. 'It is not a function of the claims to specifically exclude . . . possible inoperative substances . . . .' In re Dinh-Nguyen, 492 F.2d 856, 858-59, 181 U.S.P.Q. (BNA) 46, 48 (C.C.P.A. 1974) (emphasis omitted). Accord, In re Geerdes, 491 F.2d 1260, 1265, 180 U.S.P.Q. (BNA) 789, 793 (C.C.P.A. 1974); In re Anderson, 471 F.2d 1237, 1242, 176 U.S.P.Q. (BNA) 331, 334-35 (C.C.P.A. 1973). . . Du Pont contends

> that, because the '978 examples are 'merely prophetic', they do not aid one skilled in the art in making the invention. Because they are prophetic, argues Du Pont, there can be no guarantee that the examples would actually work. Use of prophetic examples, however, does not automatically make a patent non-enabling. The burden is on one challenging validity to show by clear and convincing evidence that the prophetic examples together with other parts of the specification are not enabling. *Atlas Powder Co. v. E. I. Du Pont de Nemours & Co.*, 750 F.2d 1569, 1576-1577 (Fed. Cir. 1984)

As indicated above, the Examiner has not properly indicated how the specification and in particular the present examples, even if prophetic, are not enabling. Absent such an indication, the cited claims are deemed enabled.

In view of the foregoing remarks, removal of the present rejection is respectfully requested at this time.

V. Claims 10, 11, 20, and 23 Are Patentable over Bauman

Claims 10, 11, 20, and 23 stand rejected under § 103(a) over Bauman. Applicants respectfully traverse the rejection.

At the outset, Applicants believe the Examiner intends the present rejection to be limited to claims 10, 11, 20, and 33 (and not 23) in view of the previous rejection made in the Office Action dated June 25, 2004. As such, the following discussion concerns claims 10, 11, 20, and 33.

Applicants would like to take this opportunity to clarify the record, as the Examiner has perhaps unintentionally mischaracterized Applicants' position with respect to Bauman. At page 4 of the Office Action, the Examiner states, "Applicants first state that prior art compound pointed out in Bauman does not read on the instant claims. True, but the instant rejection was not under 102 but rather 103. Novelty does not negate obviousness." Applicants, however, made it clear that the

present rejection is indeed under § 103, which is apparent from the following remarks summarized from Applicants' previous Amendment and Response dated September 27, 2004: (i) Bauman fails to *teach or suggest* each and every element defined by claim 20 (see page 25 of Response); (ii) the difference between the Bauman substituent [alkoxycarbonylalkylcarbonylaminoalkyl at page 52] and the presently cited substituent is not obvious (see page 26 of Response); (iii) Bauman does not teach or suggest a modification to arrive at the compounds defined by claim 20 (see page 27 of Response); (iv) absent such a teaching or suggestion, there is no reasonable expectation of success (see page 28 of Response). Certainly then, Applicants were not merely attempting to assert that novelty negates obviousness, but rather demonstrated with clear reasoning why Bauman does not render the cited claims *prima facie* obvious.

In the present Office Action at page 4, the Examiner asserts that the moiety "alkoxycarbonylalkylaminoalkyl" is still present as a choice for R^5 and it only differs from the species previously pointed out in lacking the "carbonyl" in the middle of the complex moiety. Without admitting or denying the Examiner's assertion, claims 20 and 33 are currently amended to delete the group $(C_1\text{-}C_6)$alkoxycarbonyl$(C_1\text{-}C_6)$alkylamino$(C_1\text{-}C_6)$alkyl solely to advance prosecution of the present application. Removal of the present rejection is respectfully requested at this time.

VI. Conclusion

Having addressed all outstanding issues, Applicants kindly request removal of all rejections and allowance of all pending claims at this time. To the extent the Examiner believes that it would facilitate allowance of this case, the Examiner is urged to call the undersigned at the number below.

The Commissioner is hereby authorized by this paper to charge any required fees or credit any overpayment to Deposit Account 16-1445. In particular, the Commissioner is hereby authorized by this paper to charge the fee under 37 C.F.R. § 1.17(e), as required by the Request for Continued Examination filed herewith.

Respectfully submitted,

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